Predictors of satisfactory improvements in pain for patients with early rheumatoid arthritis in a treat-to-target study

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Abstract

Objective. The aim of this study was to identify baseline predictors of achieving patient-perceived satisfactory improvement (PPSI) in pain after 6 months of treat to target in patients with early RA.

Methods. Baseline and 6 month data were used from patients included in the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. Simple and multivariable logistic regression analyses were used to identify significant predictors of achieving an absolute improvement of 30 mm or a relative improvement of 50% on a visual analogue scale for pain.

Results. At 6 months, 125 of 209 patients (59.8%) achieved an absolute PPSI and 130 patients (62.2%) achieved a relative PPSI in pain. Controlling for baseline pain, having symmetrical arthritis was the strongest independent predictor of achieving an absolute [odds ratio (OR) 3.17, P = 0.03] or relative (OR 3.44, P = 0.01) PPSI. Additionally, anti-CCP positivity (OR 2.04, P = 0.04) and having ≤12 tender joints (OR 0.29, P = 0.01) were predictive of achieving a relative PPSI. The total explained variance of baseline predictors was 30% for absolute and 18% for relative improvements, respectively.

Conclusion. Symmetrical joint involvement, anti-CCP positivity and fewer tender joints at baseline are prognostic signs for achieving satisfactory improvement in pain after 6 months of treat to target in patients with early RA.

Key words: rheumatoid arthritis, pain, disease-modifying anti-rheumatic drugs, cohort study.

Introduction

Treatment strategies in RA have shifted towards early diagnosis, close monitoring of disease activity and intensive use of DMARDs aimed at inducing rapid and sustained suppression of disease activity [1, 2]. These so-called tight control or treat-to-target (T2T) strategies have shown that clinical remission is now an achievable therapeutic goal in RA in both randomized controlled trials and daily clinical practice [3].

In these T2T strategies, the monitoring and evaluation of treatment efficacy are usually based on traditional clinical parameters or composite indices of disease activity, with a strong emphasis on joint counts and acute phase reactants. For RA patients themselves, however, pain is usually the most important priority for improvement [4, 5] and the single most important determinant of perceived disease activity [6]. Moreover, clinically significant pain may
continue among a substantial proportion of patients in clinical remission [7]. This underscores the relevance of evaluating meaningful pain relief from the patient’s perspective and its predictors in addition to changes in disease activity in the context of T2T studies and clinical practice in early RA.

Patient-perceived satisfactory improvement (PPSI) in pain is the minimal amount of improvement needed for patients to consider themselves satisfactorily improved and is defined as an improvement of ~30 mm or 50% on a 100 mm visual analogue scale (VAS) for pain [8]. Identifying prognostic factors of PPSI could provide clues for further improvement or tailoring of T2T therapy. As opposed to predictors of improvements in disease activity or predictors of remission [9, 10], however, little empirical work has examined prognostic factors of meaningful pain improvement in RA patients with early disease. Therefore the aim of this study was to examine predictors of achieving PPSI in pain after 6 months of T2T therapy in patients with early RA.

Methods

Patients

Data were used from early RA patients participating in the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study [11, 12]. The remission induction cohort consists of patients with a clinical diagnosis of RA and symptom duration of ≤ 1 year following a T2T strategy aimed at achieving fast remission. The strategy has been shown to be highly effective, with nearly half of the patients achieving clinical remission within 6 months of treatment [11]. More extensive information about the treatment protocol and the actual medication use of the patients has been reported elsewhere [11, 12]. At the time of the study, complete baseline and 6 month follow-up clinical, laboratory and patient-reported outcomes data were available for 263 patients. Data of 209 patients with a baseline pain score sufficient to be able to achieve absolute PPSI (VAS ≥ 30 mm) were selected for analysis. The median time between completion of the assessments was 25 weeks (interquartile range (IQR) 22–27). No ethical approval was required for the remission induction cohort study as evaluated by the ethics committees of the participating hospitals.

Data collection

The following variables were collected at baseline: sex, age, symptom duration, BMI, individual components of the 1987 ACR criteria for the classification of RA (morning stiffness, arthritis in three or more joint areas, arthritis of the hand joints, symmetrical arthritis, s.c. nodules, RF positivity, X-ray changes with joint erosions) [13], CRP and anti-CCP positivity. At baseline and every follow-up visit, a trained rheumatology nurse completed the 28-joint DAS (DAS28) [14], which includes a tender joint count (TJC-28), swollen joint count (SJC-28), ESR and a patient-reported rating for current general health on a 100 mm VAS (0 = very good, 100 = very poor). DAS28 scores range between 0 and 10, with a score < 2.6 indicating clinical remission [15].

At baseline and every 3 months, patients additionally completed a 100 mm VAS for pain in the past week (0 = no pain, 100 = unbearable pain), the 36-item Short Form Health Survey version 2 (SF-36v2) and the HAQ Disability Index (HAQ-DI). The SF-36v2 assesses different aspects of health status [16, 17]. Item scores can be aggregated into physical and mental component summary scores. The scales and summary scores range from 0 to 100, with higher scores representing better health status. The component summary scores are standardized using normative data from the 1998 US general population with a mean score of 50 (S.D. 10) [18]. The HAQ-DI contains 20 items measuring physical disabilities over the past week in eight categories of daily living [19, 20]. Items are scored from 0 (without any difficulty) to 3 (unable to do). A total score is calculated by averaging the highest score in each category (corrected for the use of aids and devices) if at least six categories are completed.

Statistical analyses

Potential baseline predictors considered were sex, age, symptom duration, body weight, fulfilling the 1987 ACR classification criteria, RF positivity, anti-CCP positivity, disease activity measures, general health, pain, disability and physical and mental health status. Total DAS28 scores were dichotomized into low–moderate (DAS28 < 5.1) and high disease activity (DAS28 ≥ 5.1) [21]. ESR > 28 mm/h and CRP level > 20 mg/l were categorized as elevated based on commonly used criteria for active RA. The SJC-28 and TJC-28 were plotted against absolute disease activity of > 12 joints for both joint counts. Analysis of predictors of absolute PPSI (≥ 30 mm improvement) or relative PPSI (≥ 50% improvement) in pain at 6 months was carried out using simple binary logistic regression analyses. First, univariable odds ratios (ORs) and 95% CIs were calculated for possible predictors of absolute PPSI (VAS ≥ 30 mm) or relative pain improvements to determine the level of articular involvement at which a possible association was obtained, yielding cut-off values for elevated disease activity of > 12 joints for both joint counts. Analysis of predictors of absolute PPSI (≥ 30 mm improvement) or relative PPSI (≥ 50% improvement) in pain at 6 months was carried out using simple binary logistic regression analyses. First, univariable odds ratios (ORs) and 95% CIs were calculated for possible predictors of absolute and relative PPSI without adjustment. Next, variables with a marginal significance (P < 0.20) in the univariable analysis were included in multivariable logistic regression models after controlling for baseline pain to identify unique predictors. In case of a high correlation (Pearson r > 0.5) between two variables, the predictor with the strongest univariable association with the outcome was retained in the multivariable regression model. The explained variance for both models was examined using Nagelkerke’s pseudo $R^2$. Statistical significance was defined as $P < 0.05$ (two tailed). All analyses were performed with SPSS version 20 (IBM, Armonk, NY, USA).

Results

Patient characteristics and 6 month follow-up

Table 1 summarizes the patients’ baseline characteristics and study outcomes over 6 months. Patients had active...
disease at baseline, as demonstrated by the elevated DAS28 scores, ESR and CRP level. Approximately 20% of the patients did not meet four or more of the seven ACR classification criteria for RA. Both clinical and patient-reported outcome measures improved significantly during the first 6 months of treatment. Mean DAS28 scores decreased to 2.9, with 91 (43.5%) patients achieving remission (DAS28 < 2.6). Average self-reported pain scores decreased by >50%. In total, 125 (59.8%) patients achieved an absolute PPSI of 30 mm and 130 (62.2%) patients a relative PPSI of 50% on the VAS for pain. Of the 91 patients with DAS28 remission, 21 (23.1%) and 15 (16.5%) patients, respectively, did not achieve an absolute or relative PPSI.

Univariable associations with satisfactory improvements

As expected, baseline pain intensity was more strongly associated with achieving absolute PPSI than with relative PPSI at 6 months (Table 2). Other univariable predictors of absolute PPSI were elevated ESR and general health. High disease activity, fulfilling four or more ACR criteria and symmetrical arthritis showed a marginal ($P < 0.20$) association with absolute PPSI. Statistically significant associations with relative PPSI at 6 months were seen for fulfilling the 1987 ACR criteria, symmetrical joint involvement, anti-CCP positivity and elevated ESR. Higher baseline pain, RF positivity, erosive disease, elevated CRP, $\leq 12$ tender joints and $>12$ swollen joints were marginally associated with relative PPSI. Finally, neither absolute nor relative improvements were associated with demographic variables, BMI, symptom duration or patient-reported disability and health status.

Multivariable predictors of satisfactory improvements

Since baseline pain and general health ($r = 0.53$), symmetrical arthritis and fulfilling four or more of the 1987 ACR criteria ($r = 0.58$), ESR and CRP ($r = 0.53$) and RF and anti-CCP positivity ($r = 0.62$) were strongly intercorrelated, general health, fulfilling the ACR criteria, CRP and RF were not included as predictors in the multivariable models. In the adjusted models, symmetrical joint involvement was a strong predictor of achieving both absolute and relative PPSI (Table 3) with ORs of $\sim 3$. Besides baseline pain, no other predictors of absolute PPSI remained significant in multivariable analysis. Relative PPSI was additionally and independently associated with anti-CCP positivity (OR 2.04) and fewer tender joints (OR 0.29) at baseline. Having $>12$ tender joints at baseline ($n = 34$, 16.3%) independently reduced the odds of achieving a relative PPSI 3-fold. Erosive disease and elevated ESR and high SJC were not significantly associated with achieving relative PPSI in the multivariable model.

Discussion

The aim of the present study was to identify baseline predictors of PPSIs in pain after 6 months of T2T therapy in
patients with early RA. Symmetrical joint involvement, anti-CCP positivity and ≤12 tender joints at baseline were favourable signs for achieving satisfactory improvements. Demographic characteristics as well as patients’ baseline disability and physical and mental health status were not associated with achieving PPSI.

The finding that symmetrical involvement and anti-CCP positivity were associated with higher odds of satisfactory improvements in pain suggests that the T2T strategy is more effective for patients who already show more typical signs of persistent RA at baseline. The timely initiation of DMARD therapy demands a diagnosis of early RA or early

### Table 2 Univariate predictors of patient-perceived satisfactory improvement at 6 months

<table>
<thead>
<tr>
<th></th>
<th>PPSI absolute</th>
<th>P-value</th>
<th>PPSI relative</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td></td>
<td>OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.01 (0.56, 1.80)</td>
<td>0.983</td>
<td>0.80 (0.44, 1.47)</td>
<td>0.478</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.99, 1.03)</td>
<td>0.308</td>
<td>1.01 (0.99, 1.03)</td>
<td>0.458</td>
</tr>
<tr>
<td>Symptom duration</td>
<td>0.99 (0.97, 1.01)</td>
<td>0.387</td>
<td>1.00 (0.98, 1.02)</td>
<td>0.906</td>
</tr>
<tr>
<td>BMI</td>
<td>1.00 (0.95, 1.06)</td>
<td>0.864</td>
<td>1.01 (0.96, 1.07)</td>
<td>0.730</td>
</tr>
<tr>
<td>≥4 ACR criteria</td>
<td>1.76 (0.89, 3.45)</td>
<td>0.102</td>
<td>2.26 (1.14, 4.46)</td>
<td>0.019</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td>0.95 (0.51, 1.76)</td>
<td>0.864</td>
<td>0.99 (0.53, 1.85)</td>
<td>0.977</td>
</tr>
<tr>
<td>Three or more joint areas</td>
<td>0.99 (0.16, 6.07)</td>
<td>0.993</td>
<td>1.10 (0.18, 6.73)</td>
<td>0.918</td>
</tr>
<tr>
<td>Arthritis of the hand/wrists</td>
<td>2.57 (0.60, 11.07)</td>
<td>0.204</td>
<td>0.99 (0.23, 4.25)</td>
<td>0.986</td>
</tr>
<tr>
<td>Symmetrical arthritis</td>
<td>2.03 (0.92, 4.47)</td>
<td>0.080</td>
<td>2.29 (1.03, 5.05)</td>
<td>0.041</td>
</tr>
<tr>
<td>Rheumatoid nodules</td>
<td>0.89 (0.19, 4.06)</td>
<td>0.875</td>
<td>0.80 (0.17, 3.65)</td>
<td>0.769</td>
</tr>
<tr>
<td>RF positive</td>
<td>0.88 (0.50, 1.54)</td>
<td>0.654</td>
<td>1.91 (0.81, 4.50)</td>
<td>0.140</td>
</tr>
<tr>
<td>Erosive disease</td>
<td>1.49 (0.66, 3.36)</td>
<td>0.331</td>
<td>1.72 (0.98, 3.04)</td>
<td>0.061</td>
</tr>
<tr>
<td>Anti-CCP positive</td>
<td>1.38 (0.76, 2.51)</td>
<td>0.292</td>
<td>2.17 (1.18, 3.99)</td>
<td>0.013</td>
</tr>
<tr>
<td>High disease activity (DAS28 &gt;5.1)</td>
<td>1.70 (0.97, 3.00)</td>
<td>0.065</td>
<td>0.95 (0.54, 1.68)</td>
<td>0.871</td>
</tr>
<tr>
<td>Elevated ESR (&gt;28 mm/h)</td>
<td>1.86 (1.05, 3.28)</td>
<td>0.033</td>
<td>1.89 (1.06, 3.36)</td>
<td>0.030</td>
</tr>
<tr>
<td>Elevated CRP (&gt;20 mg/l)</td>
<td>1.61 (0.88, 2.96)</td>
<td>0.282</td>
<td>1.51 (0.82, 2.80)</td>
<td>0.188</td>
</tr>
<tr>
<td>Elevated TJC (&gt;12 joints)</td>
<td>0.71 (0.34, 1.50)</td>
<td>0.373</td>
<td>0.96 (0.91, 1.00)</td>
<td>0.064</td>
</tr>
<tr>
<td>Elevated SJC (&gt;12 joints)</td>
<td>1.03 (0.98, 1.08)</td>
<td>0.260</td>
<td>1.72 (0.84, 3.54)</td>
<td>0.138</td>
</tr>
<tr>
<td>VAS general health</td>
<td>1.02 (1.04, 1.08)</td>
<td>0.003</td>
<td>1.00 (0.99, 1.02)</td>
<td>0.652</td>
</tr>
<tr>
<td>VAS pain</td>
<td>1.06 (1.01, 1.03)</td>
<td>&lt;0.001</td>
<td>1.01 (1.00, 1.03)</td>
<td>0.103</td>
</tr>
<tr>
<td>HAQ-DI score</td>
<td>1.22 (0.79, 1.88)</td>
<td>0.365</td>
<td>0.92 (0.59, 1.42)</td>
<td>0.698</td>
</tr>
<tr>
<td>SF-36v2 PCS score</td>
<td>1.00 (0.96, 1.03)</td>
<td>0.806</td>
<td>1.02 (0.98, 1.06)</td>
<td>0.317</td>
</tr>
<tr>
<td>SF-36v2 MCS score</td>
<td>0.99 (0.96, 1.01)</td>
<td>0.233</td>
<td>1.00 (0.98, 1.03)</td>
<td>0.957</td>
</tr>
</tbody>
</table>

DAS28: 28-joint DAS; HAQ-DI: HAQ Disability Index; OR: odds ratio; MCS: mental component summary; PCS: physical component summary; PPSI: patient-perceived satisfactory improvement; SF-36v2: 36-item Short Form Health Survey version 2; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale.

### Table 3 Multivariable predictors of patient-perceived satisfactory improvement at 6 months

<table>
<thead>
<tr>
<th></th>
<th>PPSI Absolute</th>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td></td>
<td>OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>VAS pain</td>
<td>1.06 (1.04, 1.09)</td>
<td>&lt;0.001</td>
<td>1.01 (0.99, 1.03)</td>
<td>0.325</td>
</tr>
<tr>
<td>Symmetrical arthritis</td>
<td>3.17 (1.13, 8.89)</td>
<td>0.029</td>
<td>2.88 (1.14, 7.27)</td>
<td>0.026</td>
</tr>
<tr>
<td>Erosive disease</td>
<td>—</td>
<td>—</td>
<td>2.47 (0.83, 7.38)</td>
<td>0.106</td>
</tr>
<tr>
<td>Anti-CCP positive</td>
<td>—</td>
<td>—</td>
<td>2.04 (1.03, 4.03)</td>
<td>0.041</td>
</tr>
<tr>
<td>High disease activity (DAS28 &gt;5.1)</td>
<td>0.73 (0.36, 1.48)</td>
<td>0.381</td>
<td>0.73 (0.36, 1.48)</td>
<td>0.381</td>
</tr>
<tr>
<td>Elevated ESR (&gt;28 mm/h)</td>
<td>1.80 (0.93, 3.47)</td>
<td>0.082</td>
<td>1.55 (0.81, 2.96)</td>
<td>0.190</td>
</tr>
<tr>
<td>Elevated TJC (&gt;12 joints)</td>
<td>—</td>
<td>—</td>
<td>0.29 (0.11, 0.75)</td>
<td>0.010</td>
</tr>
<tr>
<td>Elevated SJC (&gt;12 joints)</td>
<td>—</td>
<td>—</td>
<td>2.12 (0.83, 5.41)</td>
<td>0.116</td>
</tr>
<tr>
<td>Nagelkerke $R^2$</td>
<td>0.30</td>
<td>0.18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DAS28: 28-joint DAS; OR: odds ratio; PPSI: patient-perceived satisfactory improvement; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale.
arthrits at risk of developing into persistent and/or erosive disease [22]. Consequently, patient inclusion was based on a clinical diagnosis by the rheumatologist without regard to the 1987 ACR classification criteria for RA, which have been shown to have low specificity in recent-onset arthritis [23]. Although other recent T2T studies in early RA populations showed similar proportions of patients not fulfilling the ACR classification criteria at baseline, these strategies do come at the risk of including patients whose symptoms are driven by non-RA factors or who may not develop persistent RA.

Several previous studies have tried to identify predictors of persistence in patients with early arthritis. Anti-CCP antibody has been frequently reported to have high specificity for established RA. In patients with very early inflammatory arthritis, Raza et al. [24] showed that it also had 99% specificity in predicting the development of persistent RA. In another study, anti-CCP had the strongest independent association with the development of persistent erosive arthritis [25]. The prognostic value of anti-CCP and RF in patients with early arthritis is recognized by their high weight in the new 2010 classification criteria, which were specifically developed to enable better diagnosis and treatment early in the course of disease [26]. The current findings additionally suggest that symmetry, which is no longer a feature in these new criteria, may also have an independent value in the identification and selection of early RA patients suitable for T2T therapy. This corresponds with previous findings that symmetrical arthritis and anti-CCP seropositivity are significant independent predictors of persistent RA [26].

The finding that patients with a high number of tender joints are less likely to achieve a satisfactory improvement in pain has not been previously reported, but is consistent with previous studies pertaining to disease remission in early RA [27, 28]. Although the reason for this association cannot be determined from the present study, it may point to the inclusion of patients whose symptoms are influenced by factors other than RA. Besides disease activity, a disproportionate number of tender joints could be indicative of secondary FM [29, 30], which has been estimated to occur in 14–20% of RA patients and which has a high incidence in the first months of the disease [31]. Pollard et al. [32] specifically used TJC minus SJC as a surrogate indicator of fibromyalgic RA and showed that these patients had worse functional outcomes. In the present study, the 34 (16.3%) patients with >12 tender joints had significantly more tender than swollen joints, whereas the opposite was true for the other patients. As patients with secondary FM are unlikely to optimally benefit from pharmacological therapy aimed at reducing inflammation alone, this finding deserves further study and future early arthritis studies could focus more on identifying these patients.

Achieving PPSI in pain was not associated with any other patient-related factors, including sex, age, symptom duration or health status. Female sex has been frequently associated with more pain [33, 34] and smaller pain improvements [35, 36] in (early) arthritis. Although female sex was significantly and independently predictive of less relative improvement in the current study as well (data not shown), this did not translate into a significantly smaller proportion of females achieving 50% improvement. As the symptom duration was <1 year for all patients, this may have provided insufficient variance to be associated with outcome. Interestingly, satisfactory improvements were also unrelated to mental health status, which is in contrast to previous studies that found psychological distress to be predictive of pain outcomes in inflammatory arthritis [37–39]. Since the mental health component of the SF-36 summarizes diverse psychosocial aspects of health, univariate associations with the separate mental health, role-emotional, social functioning and vitality subscales were examined as well (data not reported). Nonetheless, none of these scales, including the mental health scale, which measures symptoms of depression and anxiety, were associated with achieving PPSI after the first 6 months of T2T.

Although these findings could be interpreted as support for the general applicability or efficacy of T2T strategies in early RA in terms of pain improvement, it should be noted that the relatively low explained variance of both models may also result from the omission of other relevant predictors in the present study. The study was highly exploratory in nature and no specific hypotheses were tested. Moreover, important variables that have been found in previous studies to be related to pain and improvement in pain were not assessed in this study. Such variables include, for example, co-morbidities, but also other psychosocial factors such as pain coping and social support [35, 40], which are not addressed in the SF-36. Consequently the present findings should be considered tentative and should be interpreted with caution. Future studies should replicate these results and further explore the predictive value of other possibly relevant variables.

The previously established cut-offs of 30 mm or 50% associated with PPSI were used to define meaningful improvements in pain in the current study [8]. Over the years, however, various cut-off values have been proposed for clinically relevant differences in pain, based on different definitions, clinical settings and methodological approaches [41, 42]. The magnitude of change required to achieve PPSI is larger than that for many other thresholds for clinically relevant change, such as the recently proposed 15 mm or 20% improvement criterion for the minimal clinically important improvement [43]. However, the thresholds for PPSI correspond closely with those defined for concepts such as adequate pain treatment [44], considerable improvement [45] and important improvement or recovery [46] and have clinical intuitive appeal [47]. Moreover, the PPSI cut-offs meet the need for definite, relevant response criteria as opposed to minimal detectable responses [48–50], which now appear realistic and appropriate considering the drastically improved outcomes of current RA treatments.

Finally, the most important predictor of absolute improvement was initial baseline pain intensity, which may have suppressed other possible associations.
The association between achieving absolute PPSI and baseline pain is not surprising given the possible psycho-physical and statistical phenomena involved in using absolute meaningful differences [51] and seems to confirm previous findings that meaningful changes are best represented as a percentage change from baseline [8].

In sum, this study identified joint symmetry, anti-CCP positivity and fewer tender joints at baseline as independent prognostic factors for achieving satisfactory pain improvement after 6 months of T2T in early RA.

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